significantly reduces the number of mutants that must be screened. The elucidation and experimental verification of evolutionary dynamics allows the design of a new generation of evolutionary methods that maximize our ability to discover novel biological molecules for pharmaceutical and industrial applications.

It will be appreciated by persons of ordinary skill in the art that the examples herein are illustrative only, and do not limit the scope of the invention or the accompanying claims.

WE CLAIM:

1. A method for selecting a crossover location in a first biopolymer having a first polymer sequence, for recombination with one or more second biopolymers each having its own second polymer sequence, which method comprises:

identifying coupling interactions between pairs of residues in the first polymer sequence;

generating a plurality of data structures, each data structure representing a crossover mutant comprising a recombination of the first and a second polymer sequence wherein each recombination has a different crossover location;

determining, for each data structure, a crossover disruption related to the number of coupling interactions disrupted in the crossover mutant represented by the data structure; and

identifying, among the plurality of data structures, a particular data structure having a crossover disruption below a threshold,

wherein the crossover location of the crossover mutant represented by the particular data structure is the identified crossover location.

2. A method of claim 1, wherein the particular polymer sequence comprises a sequence of amino acid residues.

3. A method of claim 1, wherein the particular polymer sequence comprises a sequence of nucleotide residues.

4. A method of claim 1, wherein coupling interactions are identified by use of a coupling matrix.

5. A method of claim 1, wherein the coupling matrix is the summation of all the coupling interactions of the first polymer sequence.

6. A method of claim 1, wherein coupling interactions are identified by a determination of a conformational energy between residues.

7. A method of claim 1, wherein coupling interactions are identified by a determination of interatomic distances between residues.

8. A method of claim 6, wherein conformational energies for each of the first and second polymer sequences are determined from a three-dimensional structure for at least one of the first and second polymer sequences.

9. A method of claim 7, wherein interatomic distances for each of the first and second polymer sequences are determined from a three-dimensional structure for at least one of the first and second polymer sequences.

10. A method of claim 2, wherein coupling interactions are identified by a conformational energy between residues above a threshold.

11. A method of claim 1, wherein a coupling interaction between a pair of residues in the

first polymer sequence is disrupted in a crossover mutant wherein a coupling interaction between a pair of residues is disrupted in a crossover mutant if the identity of both residues participating in the coupling interaction is different than that which exists in any of the parents.

12. A method of claim 8, wherein a coupling interaction between a pair of residues in the first polymer sequence is disrupted in a crossover mutant wherein a coupling interaction between a pair of residues is disrupted in a crossover mutant if the identity of both residues participating in the coupling interaction is different than that which exists in any of the parents.

13. A method of claim 1, wherein the crossover disruption is the summation of all coupled interactions in the parent that are considered disrupted in the data structure representing the crossover mutant.

14. A method of claim 1, wherein the threshold is an average level of crossover disruption for the plurality of data structures.

15. A method of claim 1, wherein the threshold is at least one standard deviation below the average level for the plurality of data structures.

16. A method of claim 1, wherein the threshold is set so that approximately 7.5% of the total number of generated data structures is below the threshold.

17. A method of claim 1, wherein the threshold is set so that approximately 1% of the total number of generated data structures is below the threshold.

18. A method of claim 1, wherein the threshold is set so that approximately 0.001% of the total number of generated data structures is below the threshold.

19. A method of claim1, wherein the generation of crossover mutants comprises:

the sequence alignment of a plurality of biopolymers;

the identification of possible cut points in the biopolymer based upon regions of sequence identity identified by the sequence alignment; and

the generation of single crossover mutants based upon the identified possible cut points.

20. A method of claim 19, wherein the regions of sequence identity must contain at least 4 residues.

21. A method of claim 19, there must be at least eight residues between crossovers.

22. A method of claim 1, wherein the generation of the plurality of data structures comprises:

the sequence alignment of a plurality of biopolymers using simulated annealing with non-homologous parents;

selecting crossover locations based upon the minimization of crossover disruption, fragment size, starting number of parents; and

the generation of a plurality of data structures based upon the identified possible crossover locations.

23. A method of claim 1, wherein the generation of the plurality of data structures comprises:

choosing one of the biopolymers from the plurality of biopolymers at random;

copying the biopolymer until a possible crossover location is reached;

choosing a random number between 0 and 1;

choosing a new biopolymer from the plurality of biopolymers to copy to the offspring if the random number is below a crossover probability (P_c); and

repeating the above process until the data structure representing the crossover mutant is the desired length.

24. A method of claim 19, wherein the generation of the plurality of data structures based upon identified cut points comprises:

cutting the biopolymers in into biopolymer fragments by randomly assigning cut points with a set probability;

randomly choosing one of the biopolymer fragments as a starting parent;

randomly identifying another biopolymer fragment from the total pool of the biopolymer fragments;

ligating the identified biopolymer fragment to the parent fragment, if the identified fragment has a sequence identity cut-point at the end of the fragment; and

repeating the randomly identifying step until the data structure, representing the crossover mutant is the desired length.

25. A method for directed evolution of a polymer, which method comprises steps of:

providing a plurality of parent polymer sequences;

identifying crossover locations in the parent polymer sequences for recombination according to claim 1;

generating one or more mutant polymer sequences utilizing recombinatory techniques targeted at the identified crossover locations on the parent polymer sequences;

screening the one or more mutant sequences for the one or more properties of interest; and

selecting at least one mutant sequence where one or more properties of interest are identified.

26. A method according to claim 25, wherein the method is iteratively repeated, and wherein at least one mutant sequence selected in a first iteration is a parent sequence in a second iteration.

27. A method of claim 25, wherein the recombination techniques are selected from the group consisting of: DNA shuffling, StEP method, fragmentation and reassembly, synthesis, and random-priming recombination.

28. A computer system for analyzing a polymer sequence, which computer system comprises:

memory and a processor interconnected with the memory and having one or more software components loaded therein, wherein the one or more software components cause the processor to execute steps of a method according to claim 1.

29. A computer system of claim 28, wherein the software components comprise a database of polymer sequences.

30. A computer system of claim 28, wherein the software components comprise a database of three-dimensional structures for polymer sequences.

31. A computer program comprising a computer readable medium having one or more software components encoded in computer readable form, wherein the one or more software components may be loaded into a memory of a computer system and cause a processor interconnected with the memory to execute steps of a method according to claim 1.

32. A computer program according to claim 30, wherein the computer readable medium further has, encoded thereon in computer readable form, a database of polymer sequences.

33. A computer program according to claim 30, wherein the computer readable medium further has, encoded thereon in computer readable form, a database of three-dimensional structures for polymer sequences.

34. A computer system for analyzing a polymer sequence, which computer system comprises:

memory and a processor interconnected with the memory and having one or more software components loaded therein, wherein the one or more software components cause the processor to execute steps of a method according to claim 19.

35. A computer program comprising a computer readable medium having one or more software components encoded in computer readable form, wherein the one or more software components may be loaded into a memory of a computer system and cause a processor interconnected with the memory to execute steps of a method according to claim 19.

36. A computer system for analyzing a polymer sequence, which computer system comprises:

memory and a processor interconnected with the memory and having one or more software components loaded therein, wherein the one or more software components cause the processor to execute steps of a method according to claim 23.

37. A computer program comprising a computer readable medium having one or more software components encoded in computer readable form, wherein the one or more software components may be loaded into a memory of a computer system and cause a processor

interconnected with the memory to execute steps of a method according to claim 23.

38. A computer system for analyzing a polymer sequence, which computer system comprises:

memory and a processor interconnected with the memory and having one or more software components loaded therein, wherein the one or more software components cause the processor to execute steps of a method according to claim 24.

39. A computer program comprising a computer readable medium having one or more software components encoded in computer readable form, wherein the one or more software components may be loaded into a memory of a computer system and cause a processor interconnected with the memory to execute steps of a method according to claim 24.

40. A computer system for analyzing a polymer sequence, which computer system comprises:

memory and a processor interconnected with the memory and having one or more software components loaded therein, wherein the one or more software components cause the processor to execute steps of a method according to claim 25.

41. A method for producing hybrid polymers from two or more parent polymers comprising the steps of:

identifying structural domains of at least one parent polymer;

organizing identified domains into schema;

calculating a schema disruption profile;

selecting at least one crossover location based on the schema disruption profile; and

recombining two or more parent polymers at one or more selected crossover locations to produce at least one hybrid polymer.

42. A method of claim 41, wherein parent polymers are recombined *in silico*, *in vitro*, *in vivo*, or in any combination thereof.

43. A method of claim 41, wherein parent polymers are recombined *in silico* to produce at least one candidate hybrid polymer.

44. A method of claim 43, wherein parent polymers are physically recombined at one or more crossover locations, including at least one selected crossover location, to produce at least one hybrid polymer corresponding to a candidate hybrid polymer.

45. A method of claim 44, wherein parent polymers are physically recombined *in vitro*.

46. A method of claim 44, wherein parent polymers are physically recombined *in vivo*.

47. A method of claim 41, wherein each parent polymer comprises a polypeptide.

48. A method of claim 44, wherein each parent polymer comprises a polypeptide.

49. A method of claim 41, wherein each parent polymer comprises an oligonucleotide.

50. A method of claim 44, wherein each parent polymer comprises an oligonucleotide.

51. A method of claim 44, wherein the parent polymers are one of polypeptides and oligonucleotides, and wherein parent polymers are recombined in a directed evolution experiment.

52. A method of claim 44, comprising the step of screening hybrid polymers for one or

more properties.

53. A method of claim 51, comprising the step of screening hybrid polymers for one or more properties.

54. A method of claim 51, wherein the directed evolution experiment includes at least one protocol selected from the group consisting of fragmentation and reassembly, family shuffling, exon shuffling, StEP, ITCHY, synthesis techniques, and PCR-based techniques.

55. A method of claim 44, wherein hybrid polymers are expressed by host cells.

56. A method of claim 41, wherein hybrid polymers are expressed by host cells.

57. A method of claim 53, wherein hybrid polymers are expressed by host cells.

58. A method of claim 41, wherein crossover locations are selected from a schema disruption profile based on a prediction that the selected crossovers will tend to produce relatively less schema disruption than other crossover locations.

59. A method of claim 44, wherein crossover locations are selected from a schema disruption profile based on a prediction that the selected crossovers will tend to produce relatively less schema disruption than other crossover locations.

60. A method of claim 41, wherein crossover locations are selected based on a schema disruption threshold.

61. A method of claim 44, wherein crossover locations are selected based on a schema

disruption threshold.

62. A method of claim 51, wherein crossover locations are selected based on a schema disruption threshold.

63. A method of claim 41, wherein crossover locations are selected to preserve schema from at least one parent polymer.

64. A method of claim 41, wherein crossover locations are selected to preserve schema from a plurality of parent polymers.

65. A method of claim 44, wherein crossover locations are selected to preserve schema from at least one parent polymer.

66. A method of claim 44, wherein crossover locations are selected to preserve schema from a plurality of parent polymers.

67. A method of claim 51, wherein crossover locations are selected to preserve schema from at least one parent polymer.

68. A method of claim 51, wherein crossover locations are selected to preserve schema from a plurality of parent polymers.

69. A method of claim 44, wherein a library of candidate hybrid polymers is compared with a library of physically recombined hybrid polymers.

70. A method of claim 51, wherein the sequence space of a directed evolution experiment

is reduced based on a library of *in silico* candidate hybrid candidate sequences.

71. A method for producing a library of hybrid polymers comprising the steps of:

choosing two or more parent polymers;

identifying structural domains of at least one parent polymer;

organizing identified domains into schema;

calculating a schema disruption profile;

selecting crossover locations based on the schema disruption profile;

recombining two or more parent polymers at one or more selected crossover locations to produce a set of hybrid polymers;

repeating at least the choosing and recombining steps to produce at least one additional set of hybrid polymers; and

generating a library of hybrid polymers from the sets of hybrid polymers.

72. A method of claim 71, wherein the repeated steps comprise choosing at least one hybrid polymer as a parent polymer.

73. A method of claim 71, wherein recombining steps are performed *in silico*.

74. A method of claim 73, further comprising physically recombining parent polymers at selected crossover locations to produce hybrids in the library.

75. A method of claim 71, wherein schema are common to at least two parents.

76. A method of claim 74, wherein schema are common to at least two parents.

77. A method of claim 71, wherein a schema disruption profile is calculated based on one

or both of conformational energy and interatomic distances.

78. A method of claim 75, wherein a schema disruption profile is calculated based on one or both of conformational energy and interatomic distances.

79. A method of claim 73, wherein parent polymers are physically recombined in a directed evolution experiment.

80. A method of claim 79, wherein the directed evolution experiment includes at least one protocol selected from the group consisting of fragmentation and reassembly, family shuffling, exon shuffling, StEP, ITCHY, synthesis techniques, and PCR-based techniques.

81. A method of claim 74, further comprising screening hybrids in the library for one or more properties.

82. A method of claim 73, further comprising physically recombining parent polymers at selected crossover locations to produce hybrids in the library and screening hybrids in the library for one or more properties; and wherein the repeated steps comprise choosing at least one hybrid polymer as a parent polymer based on screening results.

83. A method of claim 41, wherein schema comprise domains identified according to sequence alignments between two or more parent polymers.

84. A method of claim 71, wherein schema comprise domains identified according to sequence alignments between two or more parent polymers.

85. A method of claim 41, wherein the crossover location comprises a crossover region.

86. A method of claim 71, wherein the crossover location comprises a crossover region.

87. A method of claim 41, wherein the schema disruption profile comprises fitness contributions of polymer residues of one or more parent polymers.

88. A method of claim 71, wherein the schema disruption profile comprises fitness contributions of polymer residues of one or more parent polymers.

89. A method of claim 41, further comprising the step of calculating a crossover disruption profile.

90. A method of claim 71, further comprising the step of calculating a crossover disruption profile.

91. A method of claim 41, further comprising restricting the selection of crossover locations based on at least one predetermined constraint.

92. A method of claim 91, wherein the predetermined constraint is based on a protocol for physically recombining the polymers.

93. A method of claim 92, wherein the predetermined constraint comprises at least one of a requirement of sequence identity between parents, a constraint on the number of crossovers, and a constraint on the location of crossovers.

94. A method of claim 41, further comprising the steps of generating a coupling matrix and using the matrix in at least one of the identifying, organizing, calculating, and selecting steps.

95. A method of claim 71, further comprising the steps of generating a coupling matrix and using the matrix in at least one of the identifying, organizing, calculating, and selecting steps.

96. A method of claim 41, wherein domains are identified based on sequence information for at least one parent polymer.

97. A method of claim 71, wherein domains are identified based on sequence information for at least one parent polymer.

98. A method of claim 41, wherein domains are identified based on a crystal structure for at least one parent polymer.

99. A method of claim 71, wherein domains are identified based on a crystal structure for at least one parent polymer.

100. A method of claim 71, wherein crossover locations are selected from a schema disruption profile based on a threshold disruption value.

101. A method for modeling the recombination of two or more parent polymers comprising the steps of:

obtaining structural information for at least one parent polymer;

evaluating coupling interactions between polymer residues based on the structural information;

identifying domains based on the determined coupling interactions;

calculating the crossover disruption of the identified domains to produce a disruption profile;

applying a predetermined threshold disruption to each domain of the disruption

profile;

at least one of, accepting domains which satisfy the threshold and rejecting domains which do not satisfy the threshold;

repeating at least the identifying, calculating and applying steps until each identified domain is accepted or rejected;

designating the accepted or rejected domains as disruptive;

selecting crossover regions from domains that are not designated as disruptive; and

recombining parent polymers at selected crossover regions.

102. A method of claim 101, wherein the step of identifying domains comprises determining the polymer residues which belong to each domain, and the step of selecting crossover regions comprises specifying one or more residues within at least one non-disruptive domain.

103. A method of claim 101, wherein the threshold disruption represents a maximum allowable disruption, domains having a disruption above the threshold are accepted as disruptive and are preserved, domains having a disruption below the threshold are rejected as non-disruptive and may be altered, and crossover regions are selected from residues belonging to non-disruptive domains.

104. A method of claim 103, wherein domains having a disruption equal to the threshold are one of accepted as disruptive or rejected as non-disruptive.

105. A method of claim 102, wherein the selection of crossover regions is restricted according to one or more recombination constraints.

106. A method of claim 104, wherein the selection of crossover regions is restricted according to one or more recombination constraints.

107. A method of claim 105, wherein the constraint comprises at least one of a requirement of sequence identity between parents, a constraint on the number of crossovers, and a constraint on the location of crossovers.

108. A method of claim 106, wherein the constraint comprises at least one of a requirement of sequence identity between parents, a constraint on the number of crossovers, and a constraint on the location of crossovers.

109. A method of claim 105, wherein the constraint comprises a requirement of sequence identity between parents, and the method further comprises:

obtaining sequence information for the parent polymers;

aligning the obtained sequence information; and

identifying cut points within aligned regions of the parent sequences.

110. A method of claim 109, where the step of identifying cut points comprises selecting cut points having a relatively low crossover disruption, and the step of specifying a set of parental fragments for recombination based on selected cut points.

111. A method of claim 44, wherein parental polymers are genes, and the polymers are physically recombined by a staggered extension process (StEP) comprising the steps of:

specifying one or more selected crossover locations;

cutting each of two or more parent polymers within one or more crossover regions that each encompass one or more specified crossover locations to define a set of polymer fragments;

producing a set of defined polymer fragments, wherein each fragment has an end primer comprising a sequence with residues that extend past a specified crossover location; and

assembling at least one of pair of fragments having sequences which overlap an end primer of at least one fragment of the pair, to produce a recombinant polymer.

112. A method of claim 111, wherein the producing step comprises synthesizing two or more fragments.

113. A method of claim 112, wherein synthesizing fragments comprises split pool synthesis.

114. A method of claim 111, wherein fragments are assembled by extension from an end primer.

115. A method of claim 111, wherein the set of defined polymer fragments comprises all of the fragments arising from cutting all of the parent polymers within all of the crossover regions that encompass all of the specified crossover locations.

116. A method of claim 115, wherein all of the fragments are assembled in all of the possible combinations.

117. A method of claim 111, further comprising the step of screening one or more recombinant polymers for a property.

118. A method of claim 74, wherein parental polymers are genes, and the polymers are physically recombined by a staggered extension process (StEP) comprising the steps of:

specifying one or more selected crossover locations;

cutting each of two or more parent polymers within one or more crossover regions that each encompass one or more specified crossover locations to define a set of polymer fragments;

producing a set of defined polymer fragments, wherein each fragment has an end primer comprising a sequence with residues that extend past a specified crossover location;

assembling at least one of pair of fragments having sequences which overlap an end primer of at least one fragment of the pair, to produce a recombinant polymer.

119. A method of claim 118, wherein fragments are assembled by extension from an end primer.

120. A method of claim 111, wherein the set of defined polymer fragments comprises all of the fragments arising from cutting all of the parent polymers within all of the crossover regions that encompass all of the specified crossover locations; and wherein all of the fragments are assembled in all of the possible combinations.

121. A method of claim 44, wherein the parental polymers are genes, and the polymers are physically recombined by an *in vitro-in vivo* recombination method comprising the steps of:

shuffling at least two parent polymers to produce a set of parental fragments having selected crossover locations;

assembling fragments at crossover locations by overlap extension and gap repair, to provide double stranded sequences containing mismatched regions; and

repairing the mismatched regions *in vivo* by inserting the double-stranded sequences into a host cell to provide a library of crossover recombinants.

122. A method of claim 121, wherein the double stranded sequences are inserted into a host cell in the form of a heteroduplex plasmid.

123. A method of claim 121, wherein parental homoduplexes are removed.

124. A method of claim 44, wherein the parental polymers are genes, and the polymers are physically recombined by an *in vitro-in vivo* recombination method comprising the steps of:

specifying one or more selected cut points;

preparing synthetic polymer fragments having sequences corresponding to the sequences of parent polymers that are cut at specified cut points;

extending the sequence of each fragment at a cut point against a parental template to produce a set of polymer duplexes representing different combinations of fragments;

removing parent homoduplex polymers; and

providing a set of recombinants from the resulting heteroduplex polymers.

125. A method of claim 124, wherein parent homoduplexes are removed by inserting the polymer duplexes into a host cell.

126. A method of claim 125, wherein the polymer duplexes are inserted into a host cell in the form of a heteroduplex plasmid.

127. A method of claim 74, wherein the parental polymers are genes, and the polymers are physically recombined by an *in vitro-in vivo* recombination method comprising the steps of:

specifying one or more selected cut points;

providing polymer fragments having sequences corresponding to the sequences of parent polymers that are cut at specified cut points;

extending the sequence of each fragment at a cut point against a parental template to produce a set of polymer duplexes representing different combinations of fragments;

removing parent homoduplex polymers; and

providing a set of recombinants from the resulting heteroduplex polymers.

128. A method of claim 127, wherein parent homoduplexes are removed by inserting the

polymer duplexes into a host cell.

129. A method of claim 128, wherein the polymer duplexes are inserted into a host cell in the form of a heteroduplex plasmid.

130. A method of claim 127, further comprising the step of screening one or more recombinant polymers for a property.

131. A method of claim 44, wherein the parental polymers are genes, and the polymers are physically recombined by a PCR amplification method comprising the steps of:

specifying one or more selected cut points;

defining polymer fragments having sequences corresponding to the sequences of parent polymers that are cut at specified cut points;

providing sets of primers, wherein each primer in a set hybridizes to all parent strands at a crossover region corresponding to a specified cut point;

producing a set of defined fragments from each parent polymer by PCR amplification with each set of primers; and

assembling fragments in a pool by PCR amplification.

132. A method of claim 131, wherein:

each set of primers is a pair of terminal primers or a pair of intervening primers;

each primer in a terminal pair of primers corresponds to at least one terminal end of one parent polymer; and

each primer in each intervening pair of primers corresponds to a specified cut point.

133. A method of claim 132, wherein PCR amplification is performed using a first primer selected a first pair of primers, and a second primer selected from a second pair of primers.

134. A method of claim 133, wherein the first and second primers flank the ends of a polymer fragment.

135. A method of claim 74, wherein the parental polymers are genes, and the polymers are physically recombined by a PCR amplification method comprising the steps of:

specifying one or more selected cut points;

defining polymer fragments having sequences corresponding to the sequences of parent polymers that are cut at specified cut points;

providing sets of primers, wherein each primer in a set hybridizes to all parent strands at a crossover region corresponding to a specified cut point;

producing a set of defined fragments from each parent polymer by PCR amplification with each set of primers; and

assembling fragments in a pool by PCR amplification.

136. A method of claim 135, wherein:

each set of primers is a pair of terminal primers or a pair of intervening primers;

each primer in a terminal pair of primers corresponds to at least one terminal end of one parent polymer; and

each primer in each intervening pair of primers corresponds to a specified cut point.

137. A method of claim 136, wherein PCR amplification is performed using a first primer selected a first pair of primers, and a second primer selected from a second pair of primers.

138. A method of claim 137, wherein the first and second primers flank the ends of a polymer fragment.

139. A method of claim 131, further comprising the step of screening one or more

recombinant polymers for a property.

140. A method of claim 44, wherein the parental polymers are genes, and the polymers are physically recombined by a family shuffling method comprising the steps of:

specifying one or more selected crossover locations;

providing sets of primer pairs, wherein each primer of each pair comprises sequences from two parent polymers which span and include a specified crossover location;

producing fragments of the parent polymers;

reassembling the fragments in the presence of the primers using PCR amplification.

141. A method of claim 74, wherein the parental polymers are genes, and the polymers are physically recombined by a family shuffling method comprising the steps of:

specifying one or more selected crossover locations;

providing sets of primer pairs, wherein each primer of each pair comprises sequences from two parent polymers which span and include a specified crossover location;

producing fragments of the parent polymers;

reassembling the fragments in the presence of the primers using PCR amplification.

142. A method of producing recombinant oligonucleotides from two or more parent oligonucleotides by a staggered extension process comprising the steps of:

selecting one or more crossover locations for each parent oligonucleotide;

cutting each of two or more parents within one or more crossover regions that each encompass one or more specified crossover locations to define a set of fragments;

producing a set of defined fragments, wherein each fragment has an end primer comprising a sequence with residues that extend past a specified crossover location; and

assembling at least one of pair of fragments having sequences which overlap an end primer of at least one fragment of the pair, to produce a recombinant oligonucleotide.

143. A method of producing recombinant oligonucleotides from two or more parent oligonucleotides by an *in vitro-in vivo* recombination method comprising the steps of:

selecting one or more crossover locations for each parent oligonucleotide;

shuffling at least two parent oligonucleotides to produce a set of fragments having selected crossover locations;

assembling fragments at crossover locations by overlap extension and gap repair, to provide double stranded sequences containing mismatched regions; and

repairing the mismatched regions *in vivo* by inserting the double-stranded sequences into a host cell to provide a library of crossover recombinants.

144. A method of producing recombinant oligonucleotides from two or more parent oligonucleotides by an *in vitro-in vivo* recombination method comprising the steps of:

specifying one or more selected cut points for each parent oligonucleotide;

preparing synthetic polymer fragments having sequences corresponding to the sequences of parent oligonucleotides that are cut at specified cut points;

extending the sequence of each fragment at a cut point against a parental template to produce a set of oligonucleotide duplexes representing different combinations of fragments;

removing parent homoduplex oligonucleotides; and

providing a set of recombinants from the resulting heteroduplex oligonucleotides.

145. A method of claim 144, wherein the oligonucleotide duplexes are removed by inserting oligonucleotide duplexes into a host cell in the form of a heteroduplex plasmid.

146. A method of producing recombinant oligonucleotides from two or more parent oligonucleotides by a PCR amplification method comprising the steps of:

specifying one or more selected cut points for each parent oligonucleotide;

defining oligonucleotide fragments having sequences corresponding to the sequences

of parent oligonucleotides that are cut at specified cut points;

providing sets of primers, wherein each primer in a set hybridizes to all parent strands at a crossover region corresponding to a specified cut point;

producing a set of defined fragments from each parent by PCR amplification with each set of primers; and

assembling fragments in a pool by PCR amplification.

147. A method of claim 146, wherein:

each set of primers is a pair of terminal primers or a pair of intervening primers;

each primer in a terminal pair of primers corresponds to at least one terminal end of one parent polymer; and

each primer in each intervening pair of primers corresponds to a specified cut point.

148. A method of claim 147, wherein PCR amplification is performed using a first primer selected a first pair of primers, and a second primer selected from a second pair of primers.

149. A method of claim 148, wherein first and second primers flank the ends of a fragment.

150. A method of producing recombinant oligonucleotides from two or more parent oligonucleotides by a family shuffling method comprising the steps of:

specifying one or more selected crossover locations for each parent oligonucleotide;

providing sets of primer pairs, wherein each primer of each pair comprises sequences from two parents which span and include a specified crossover location;

producing fragments of the parent polymers;

reassembling the fragments in the presence of the primers using PCR amplification.

151. A method of claim 1, wherein a coupling interaction between a pair of residues in the

first polymer sequence is disrupted in a crossover mutant if the identity of a residue is different in the crossover mutant than in the first polymer sequence, and wherein a coupling interaction between a pair of residues is scaled by the probabilities that the identity and sequence position of the coupled residues are the same in both parents.

152. A method for producing hybrid polymers from two or more parent polymers comprising the steps of:

providing at least two parent polymers, both comprising a polypeptide or a polynucleotide;

identifying structural domains of at least one parent polymer;

organizing identified domains into schema;

calculating a schema disruption profile;

selecting at least one crossover location based on the schema disruption profile; and

recombining two or more parent polymers at one or more selected crossover locations to produce at least one library comprising at least one hybrid polymer.

153. A method of claim 152, wherein parent polymers are recombined *in silico*, *in vitro*, *in vivo*, or in any combination thereof.

154. A method of claim 153, wherein parent polymers are recombined in a directed evolution experiment.

155. A method of claim 152, wherein crossover locations are selected from a schema disruption profile based on a predicted threshold at which the structural tolerance of at least one parent polymer is lost.

156. A method of claim 152, further comprising the step of screening the library for one or

more polymer properties.

157. A method of claim 152, wherein parent polymers

are recombined *in silico* to produce at least one candidate hybrid polymer; and

are physically recombined at one or more crossover locations, including at least one selected crossover location, to produce at least one hybrid polymer corresponding to a candidate hybrid polymer.

158. A method of claim 157, wherein a library of candidate hybrid polymers is compared with a library of physically recombined hybrid polymers.

159. A method of claim 154, wherein the directed evolution experiment includes at least one protocol selected from the group consisting of fragmentation and reassembly, family shuffling, exon shuffling, StEP, ITCHY, synthesis techniques, and PCR-based techniques.

160. A method of claim 152, wherein crossover locations are selected based on a schema disruption threshold.

161. A method of claim 160, wherein each hybrid in the library comprises parent polymers that are recombined at a single crossover location.

162. A method for producing hybrid polymers from two or more parent polymers comprising the steps of:

providing at least two parent polymers, both comprising a polypeptide or a polynucleotide;

identifying structural domains of at least one parent polymer;

organizing identified domains into schema;

calculating a schema disruption profile based on a disruption threshold;

selecting at least one crossover location based on the schema disruption profile;

recombining two or more parent polymers *in silico* at one or more selected crossover locations to produce a hybrid polymer library; and

predicting one or more properties of hybrid polymers in the library.

163. A method of claim 162, wherein each hybrid in the library comprises parent polymers that are recombined at a single crossover location.

164. A method of claim 162, further comprising the step of physically recombining parent polymers at one or more crossover locations, including at least one selected crossover location, to produce at least one polymer corresponding to a hybrid polymer in the library.

165. A method of claim 162, wherein each selected crossover location corresponds to a schema disruption that is below the threshold.

166. A method of claim 152, wherein the schema disruption profile comprises counting the interactions between schema to determine groups of schema that are preserved in the hybrid polymers.

167. A method of claim 162, wherein the schema disruption profile comprises counting the interactions between schema to determine groups of schema that are preserved in the hybrid polymers.

168. A method of claim 166, wherein the polymer is an enzyme and the property of interest is enzymatic activity.

169. A method of claim 167, wherein the polymer is an enzyme and the property of interest is enzymatic activity.

170. A method of claim 152, wherein the schema disruption profile comprises counting the interactions between schema to determine groups of schema that are preserved in the hybrid polymers.

171. A method of claim 152, wherein the enzyme is beta-lactamase.

172. A beta-lactamase hybrid comprising the amino acid sequence of PSE-4, substituted in part by an amino acid sequence of TEM-1, wherein the substitution is selected from the group of:

amino acid residues 164-179 of PSE-4 are replaced by the corresponding amino acid residues of TEM-1;

amino acid residues 190-216 of PSE-4 are replaced by the corresponding amino acid residues of TEM-1;

amino acid residues 71-216 of PSE-4 are replaced by the corresponding amino acid residues of TEM-1;

amino acid residues 71-130 of PSE-4 are replaced by the corresponding amino acid residues of TEM-1; and

amino acid residues 254 and higher of PSE-4 are replaced by the corresponding amino acids of TEM-1.

173. A beta-lactamase hybrid comprising the amino acid sequence of TEM-1, substituted in part by an amino acid sequence of PSE-4, wherein the substitution is selected from the group of:

amino acid residues 164-179 of TEM-1 are replaced by the corresponding amino acid

residues of PSE-4;

amino acid residues 190-216 of TEM-1 are replaced by the corresponding amino acid residues of PSE-4;

amino acid residues 71-216 of TEM-1 are replaced by the corresponding amino acid residues of PSE-4;

amino acid residues 71-130 of TEM-1 are replaced by the corresponding amino acid residues of PSE-4; and

amino acid residues 254 and higher of TEM-1 are replaced by the corresponding amino acids of PSE-4.

174. A hybrid polymer comprising a first polypeptide recombined with at least a second polypeptide at one or more crossover locations selected according to a schema disruption threshold.

175. A hybrid polymer of claim 174, wherein the threshold is based on counting the number of interactions between schema in a schema disruption profile.